Multiple myeloma (MM) is a tumor originating from the terminally differentiated B cells. It develops mainly in elderly patients and leads to compromised immune system, hypercalcemia, and end-organ damage typically encompassing renal failure, anemia, or bone lesions. Although the therapeutic efficacy of novel drugs for MM has improved over recent years MM remains a largely incurable disease, with a median survival of up to 6 years. Intriguingly, the improvements in anticancer efficacy of novel therapeutic approaches are associated with increased rate of other organ injuries. For example, cardiovascular diseases resulting from anticancer treatments have now become the second leading cause of long-term morbidity among cancer survivors. Therefore, identification of combinations of therapeutic approaches that would exert potentiated antitumor effects and at the same time would specifically reduce treatment-related toxicity are of paramount importance. We have previously shown that bortezomib, which is a proteasome inhibitor used in the treatment of MM patients, is cardiotoxic. It seems that at least to some extent the bortezomib-associated cardiotoxicity is related to decreased nitric oxide (NO) synthesis in endothelial cells. Our unpublished results indicate that sildenafil, which is triggering NO signaling pathway, is ameliorating bortezomib-induced cardiotoxicity, further confirming potentially beneficial effects of NO. Nitric oxide is produced in enzymatic reaction from an amino acid L-arginine. Coincidentally, L-arginine is also a substrate for arginase-1 (Arg-1), an enzyme involved in L-arginine degradation. In our preliminary studies, we have observed that Arg-1 inhibitor co-developed by our research team is increasing NO concentrations in mice. Therefore, we wish to investigate whether turning off Arg-1 activity might reduce bortezomib-induced cardiotoxicity, by providing increased L-arginine concentrations for NO synthesis. Moreover, the published data as well as our preliminary findings demonstrate that Arg-1 is interfering with the development of effective immune response against various types of tumors. However, the role of Arg-1 has not been extensively studied in MM. Thus, using both genetically engineered models as well as Arg-1 inhibitor, we plan to determine whether Arg-1 is a potentially druggable target in the management of MM. We will investigate whether lack of or pharmacological inhibition of Arg-1 is regulating anti-MM immune response, affecting the rate of MM progression and potentiating antitumor effects of bortezomib. This knowledge is necessary to better understand molecular mechanisms involved in the development of MM-associated immune response. The results of this project might also be helpful in identifying novel targets for cancer treatment, better understanding of the shortcomings and adverse effects observed in cancer patients undergoing cancer treatment and in finding novel areas to be exploited in the fields of immunology, cardiooncology and experimental oncology.